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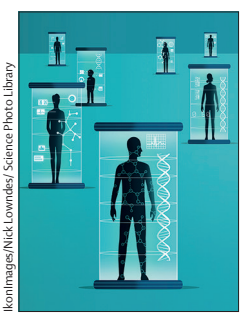
IFNL4 and donor selection for matched unrelated donor haematopoietic stem-cell transplantation



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The selection of an optimal donor is an essential element in ensuring the best possible outcome for patients undergoing allogeneic haematopoietic stem-cell transplantation. HLA matching of donors and recipients represented a major milestone contributing substantially to the first successful transplant outcomes. Although the earliest allogeneic transplantations relied primarily on HLA-matched sibling donors, expansion of the donor pool for those without a suitably matched sibling donor soon emerged as an unmet need and led to the establishment of donor registries in the 1980s, which now list in excess of 32 million potential donors worldwide.[1] Over the past 20 years, the widespread adoption of high-resolution allele-level HLA typing has led to marked improvements in outcomes following matched unrelated donor transplantation. Notably, the degree of high-resolution HLA match remains the most important donor-specific predictor of matched unrelated donor outcomes, with a roughly 10% decline in overall survival associated with each successive mismatch at *HLA-A, HLA-B, HLA-C,* and *HLA-DRB1* loci, primarily due to increased treatment-related mortality.[2] Although matching at *HLA-DQB1* has not been shown to have a substantial effect on outcomes, retrospective analyses have shown that non-permissive mismatching at the class II *HLA-DPB1* locus could result in excess overall and non-relapse mortality, as well as graft-versus-host disease (GVHD).[3] It has also been reported that optimisation of the killer-cell immunoglobulin-like receptor (KIR) complex encoding genes that recognise specific HLA class I epitopes (KIR ligands) in unrelated donors could affect outcomes by reducing post-transplant relapse, particularly in acute myeloid leukaemia, through selection of KIR B donor haplotypes containing one or more activating KIR receptors.[4,5] Other considerations in unrelated donor selection include the optimisation for donor cytomegalovirus status, younger age, gender, parity, and ABO blood type.[6]

In *The Lancet Haematology*, Shahinaz Gadalla and colleagues[7] present the results of a retrospective analysis of patients with acute myeloid leukaemia or acute lymphocytic leukaemia who underwent myeloablative 10/10 HLA-matched unrelated donor transplantation to assess the effect of both donor and recipient interferon lambda 4 (*IFNL4*) genotype on outcomes.[7]

Interferons are a group of immunomodulatory cytokines with essential involvement in both the innate and adaptive host response to viral infection. IFNλ4 is a type III interferon highly conserved among higher mammals, whose discovery in 2013 was triggered by the observation of enhanced hepatitis C virus (HCV) clearance in some individuals in association with a genetic marker ultimately mapped to the *IFNL4* gene locus.[8] IFNλ4 has been shown to exert potent antiviral activity against HCV as well as a host of other viruses in vitro, including West Nile virus, dengue virus, and coronaviruses, and has also been shown to exert a negative immunomodulatory effect to dampen the interferon response.[9] Paradoxically, despite its antiviral activity, the genetic marker associated with improved HCV clearance has been shown to insert a premature stop codon within the first exon of the *IFNL4* open reading frame, creating a null phenotype, the prevalence of which varies substantially among different populations.[8]

On the basis of these observations, and in recognition of the central role of the immune system in mediating essential post-transplantation processes including GVHD, response to infection, and clearance of tumour cells, it is reasonable to speculate that IFNλ4 could have an effect on transplant outcomes. In the current study, Gadalla and colleagues assessed two cohorts of patients (discovery dataset [n=404] and validation dataset [n=1245]), and an overlapping dataset combining the two cohorts (combined dataset [n=1593]). Participants had acute myeloid leukaemia or acute lymphocytic leukaemia and underwent myeloablative 10/10 HLA-matched unrelated donor transplantation. Inclusion criteria included availability of a biorepository of pre-transplantation donor and recipient specimens as well as detailed clinical annotation, to investigate the potential effect of both

donor and recipient *IFNL4* genetic polymorphisms on outcomes. Although the authors found that the *IFNL4* genotype of the recipient had no effect on outcomes, they showed that patients who received grafts from donors with a genotype predictive of functional IFNλ4 expression had significantly worse outcomes than those with genetic variants encoding a IFNλ4-null phenotype. Specifically, they observed that non-relapse mortality, due to both infection and GVHD, was significantly reduced across both cohorts in the *IFNL4*-null donor group; *IFNL4*-positive genotype was associated with increased risk of non-relapse mortality (hazard ratio [HR] 1·60, 95% CI 1·23–2·10; p=0·0005 in the discovery dataset; 1·22, 1·05–1·40; p=0·0072 in the validation dataset; and 1·27, 1·12–1·45; p=0·0001 in the combined dataset). Similarly, an association of donor *IFNL4*-positive genotype with overall survival was seen in the discovery dataset (HR 1·24, 95% CI 1·02–1·51; p=0·034) and combined dataset (1·11, 1·02–1·22; p=0·018), but did not reach statistical significance in the validation dataset (1·10, 0·98–1·20; p=0·10). The authors speculated that the diminished effect of donor *IFNL4* genotype on overall survival in the validation dataset might have been the result of a substantially increased proportion of bone marrow stem cell donors, as opposed to peripheral blood stem cell donors in that group. It is notable that unrelated donor bone marrow stem cell recipients have been previously shown to have significantly less chronic GVHD, and improved overall survival compared with peripheral blood stem cell recipients,[10] perhaps dampening the potential benefit afforded to a *IFNL4*-null donor. The authors also reported a subgroup analysis, stratified on graft source, for non-relapse mortality, but results were not significant.

These findings are notable in that the observed improvements in outcomes were additive to those resulting from the use of what would currently be considered optimally matched donors (10/10 HLA-matched), and the magnitude of improvement as described was similar to that observed in going from a single HLA-A, HLA-B, HLA-C, or HLA-DR mismatch to a 10/10 matched donor. It is unclear what effect *IFNL4* testing would have on outcomes in the setting of concomitant optimisation for HLA-DPB1 or KIR, as data for HLA-DP matching or KIR haplotyping were not presented for the datasets studied. It is also unclear whether the effect of donor *IFNL4* genotype would extend to patients receiving an alternative GVHD prophylaxis strategy, such as post-transplant cyclophosphamide, which was not in widespread use at the time that patients in these cohorts had transplantations, or to patients undergoing alternative donor transplantations such as from mismatched unrelated, haploidentical related, or umbilical cord blood donors. Finally, although there was no significant difference in relapse based on donor IFNλ4 status in these cohorts, it is unclear whether the observed outcome benefits would apply to other transplant indications. Nonetheless, these initial observations are intriguing and might justify further investigation to better establish whether *IFNL4* genotyping warrants incorporation into the current donor selection algorithm.

I declare no competing interests.

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